



DATA AND SAFETY MONITORING PLAN

George Washington Cancer Center
George Washington University

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1. Introduction

1.1. The George Washington Cancer Center

The George Washington Cancer Center (GWCC) is a collaboration between George Washington University (GWU) Hospital, The GW Medical Faculty Associates (MFA), and the GW School of Medicine and Health Sciences (SMHC) to expand the George Washington University's (GW) efforts in the fight against cancer. The mission of the GWCC is to drive transformational research, personalized therapy, family-centered care, and cancer policy in the nation's capital.

The George Washington Cancer Center is dedicated to conducting high quality research that protects the rights, safety, and welfare of human subjects as well as ensuring the integrity of study results.

This institutional Data and Safety Monitoring Plan (DSMP) describes the framework for oversight of GWCC clinical research. Additionally, this document outlines the responsibilities of the GWCC leadership, GWCC Committees, Principal Investigators (PIs), Sub-Investigators, and other GWCC research personnel for maintaining the safety of participants in GWCC clinical research and ensuring data integrity.

The GWCC has the responsibility of clinical research oversight through the Scientific Leadership Committee (SLC). The SLC oversees the functions of GWCC's Protocol Review & Monitoring Committee (PRMC) and Data and Safety Monitoring Committee (DSMC).

To facilitate the oversight responsibilities, GWCC has constituted the PRMC and DSMC. The PRMC has the role of assessing scientific merit, confirming feasibility, prioritizing, determining risk level, and ensuring appropriate data and safety monitoring plans for GWCC clinical trials. The DSMC has the responsibility of ensuring the safety of participants and integrity of study data for GWCC Investigator-Initiated Trials (IITs).

Investigator-Initiated Trials play an important role in the research portfolio of the GWCC. GWCC investigators are responsible for both the design and conduct of their IITs. GWCC PIs must ensure compliance with this DSMP and/or a study specific DSMP.

The National Cancer Institute (NCI) mandates that NCI-designated Comprehensive Cancer Centers maintain a system for oversight of all clinical research conducted in the cancer center. Additionally, National Institutes of Health (NIH) policy requires institutions facilitating NIH-supported or NIH-conducted clinical trials have a system for oversight and monitoring the conduct of clinical trials to ensure the safety of participants and the integrity of the data. Clinical trial monitoring is critical to ensuring appropriate trial conduct, the validity and integrity of study data, protocol compliance, and patient safety. This DSMP provides the detail necessary for the PI and the institution to provide

sufficient oversight for ensuring scientific integrity, monitoring study progress, and ensuring the safety of participants. This DSMP complies with the NIH policies for data and safety monitoring.

This document describes how the GWCC ensures adequate scientific merit of each trial, institutional prioritization of trials, feasibility of performing the research at the GWCC, proper data and safety monitoring, inclusion of women, minorities and other underrepresented populations, and inclusion of individuals across the lifespan.

1.1.1. Community Outreach & Engagement

The GWCC is dedicated to serving the population in and around the Washington, DC area (the “catchment area”). Through community outreach and engagement, the GWCC focuses on the needs of the community and works to provide excellent clinical care and enhance the availability of clinical research to all populations in the catchment area. Another focus of community outreach and engagement is to address cancer prevention and health disparities. A goal of community outreach and engagement is to enhance enrollment and retention of minority, underserved, underrepresented, and special populations in GWCC research so trials better reflect all populations that may benefit from the research.

1.2. Role/Purpose of an Institutional DSMP

The purpose of this DSMP is to have a written, formalized policy for activation and oversight of clinical research conducted at the GWCC.

This DSMP describes the operations for:

- Determining institutional priority of proposed trials,
- Confirming the scientific integrity of trials,
- Confirming trials include proper data and safety monitoring plans,
- Approving trials to be activated at GWCC,
- Monitoring the scientific progress of trials,
- Monitoring accrual,
- Monitoring the safety of participants in the research,
- Assuring compliance with requirements for reporting adverse events and unanticipated problems,
- Reporting and handling temporary or permanent suspension of a trial,
- Assuring data accuracy, and
- Assuring protocol compliance.

Additionally, this DSMP includes the requirements for establishing a study specific Data and Safety Monitoring Board in [Appendix A](#).

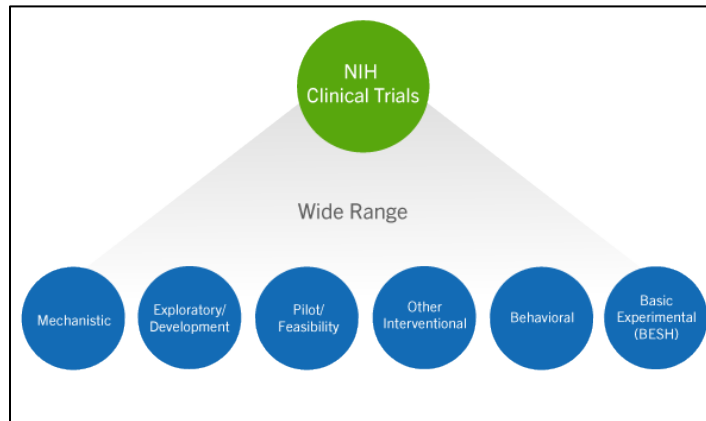
1.3. Applicability

This is the institutional DSMP and therefore applies to all types of proposed cancer-related studies at George Washington University, including those conducted outside the GWCC. Any exceptions to applicability are included in the relevant sections within this document.

NIH Definition of a Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

(<https://grants.nih.gov/policy/clinical-trials/definition.htm>)



GWCC Investigator-Initiated Trials

All GWCC IITs are subject to this DSMP for the purpose of gaining PRMC approval to activate the trial at GWCC and providing continued oversight for scientific progress and accrual. IITs may be single- or multi-site and may involve and IND or IDE. Study-specific data and safety monitoring plans must contain, at a minimum, all essential elements of a DSMP and be commensurate with the risk level, size, and complexity of the trial. Study specific DSMPs are described in the study protocol and require approval by the PRMC and an Institutional Review Board (IRB).

Industry-Sponsored Trials

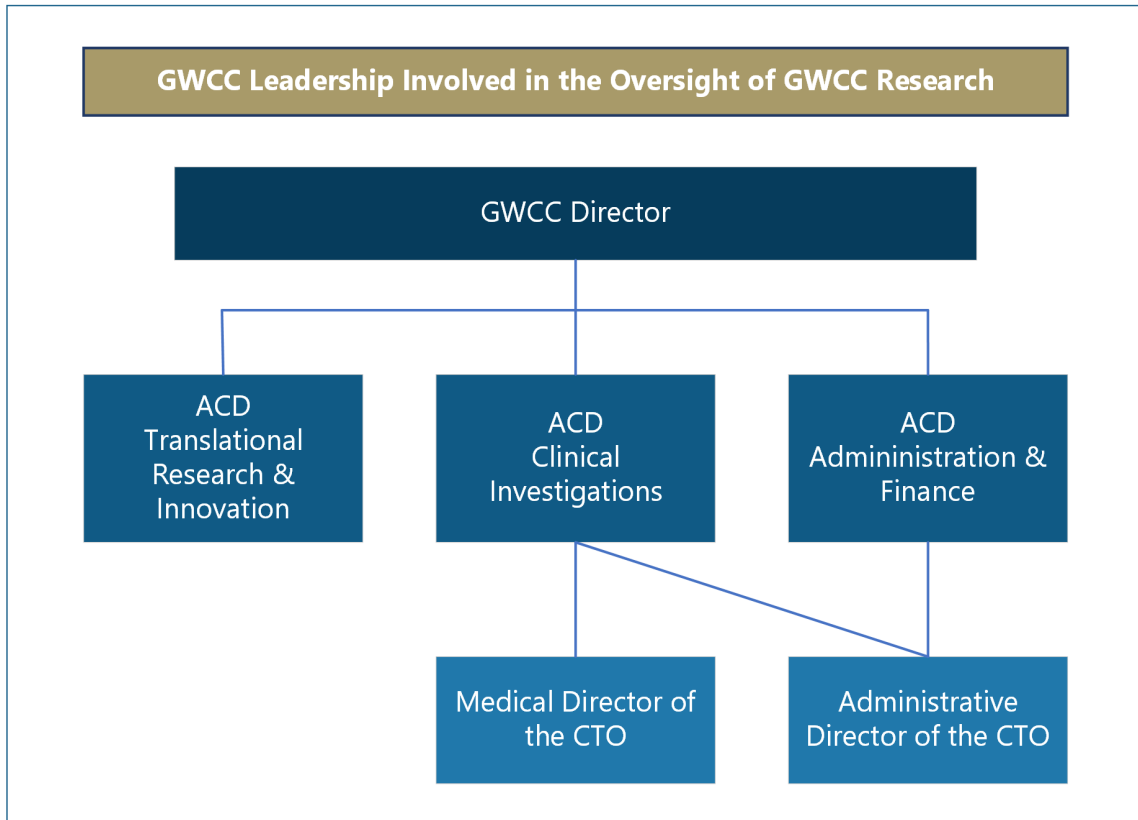
All industry-sponsored trials are subject to PRMC oversight for the purpose of gaining PRMC approval to activate the trial at the GWCC and providing continued oversight for scientific progress and accrual. The PRMC is responsible for ensuring that each industry-sponsored protocol contains an appropriate data and safety monitoring plan commensurate with the risk level, size, and complexity of the trial.

2. GWCC Administrative Infrastructure & Personnel

This section provides general information on the individuals involved in GWCC’s research oversight system.

2.1. GWCC Leadership

GWCC leadership is committed to ensuring the infrastructure and resources exist for investigators to conduct high quality research while ensuring the safety of subjects. This organizational chart includes the leadership involved in the oversight of clinical research at the GWCC.



2.2. Investigators & Clinical Research Teams (CRTs)

GWCC members with proper credentials will serve as Principal Investigators and Sub-Investigators. Investigators lead the Clinical Research Teams (CRTs). The CRTs are multidisciplinary, consisting of scientists, clinicians, nurses, pharmacists, etc., with expertise in a disease or discipline. The CRTs are supported by clinical and regulatory personnel from the Clinical Trials Office (CTO). The investigators and CRTs play a pivotal role in building the research portfolio within the disease site/discipline as well as the institution. The Investigator’s and CRT’s roles and responsibilities with respect to protocol review and monitoring, including data and safety monitoring are described elsewhere in this document, and in the PRMC and DSMC Charters.

2.3. Clinical Protocol & Data Management (CPDM): The Clinical Trials Office (CTO)

The Clinical Protocol and Data Management (CPDM) includes GWCC leadership and the GWCC Clinical Trials Office (CTO). The CTO is a centralized office that provides the personnel and comprehensive infrastructure necessary for the conduct of clinical trials involving cancer patients. The objectives of

CTO personnel are to provide central management and oversight functions for coordinating, facilitating, and reporting, whatever the study origin (local, industry, NCI NCTN, or other).

Under the direction of the GWCC leadership, the Clinical Trials Office (CTO) leadership oversees the operations for facilitating, managing, and tracking research, and the personnel responsible for these functions. Tracking of research is managed via the [GWCC Clinical Trials Management System \(CTMS\), OnCore](#).

2.3.1. CTO Medical Director

The CTO Medical Director reports to the ACD of Clinical Investigations. Through the ACD of Clinical Investigations, the CTO Medical Director assists the GWCC Director with aligning clinical research goals with those of the GWCC as a whole. This includes addressing long-term strategic plans for the CTO, and serving as a liaison between the CTO Administrative Director and the ACD of Administration and Finance and ACD of Clinical Investigations.

2.3.2. CTO Administrative Director (CTO AD)

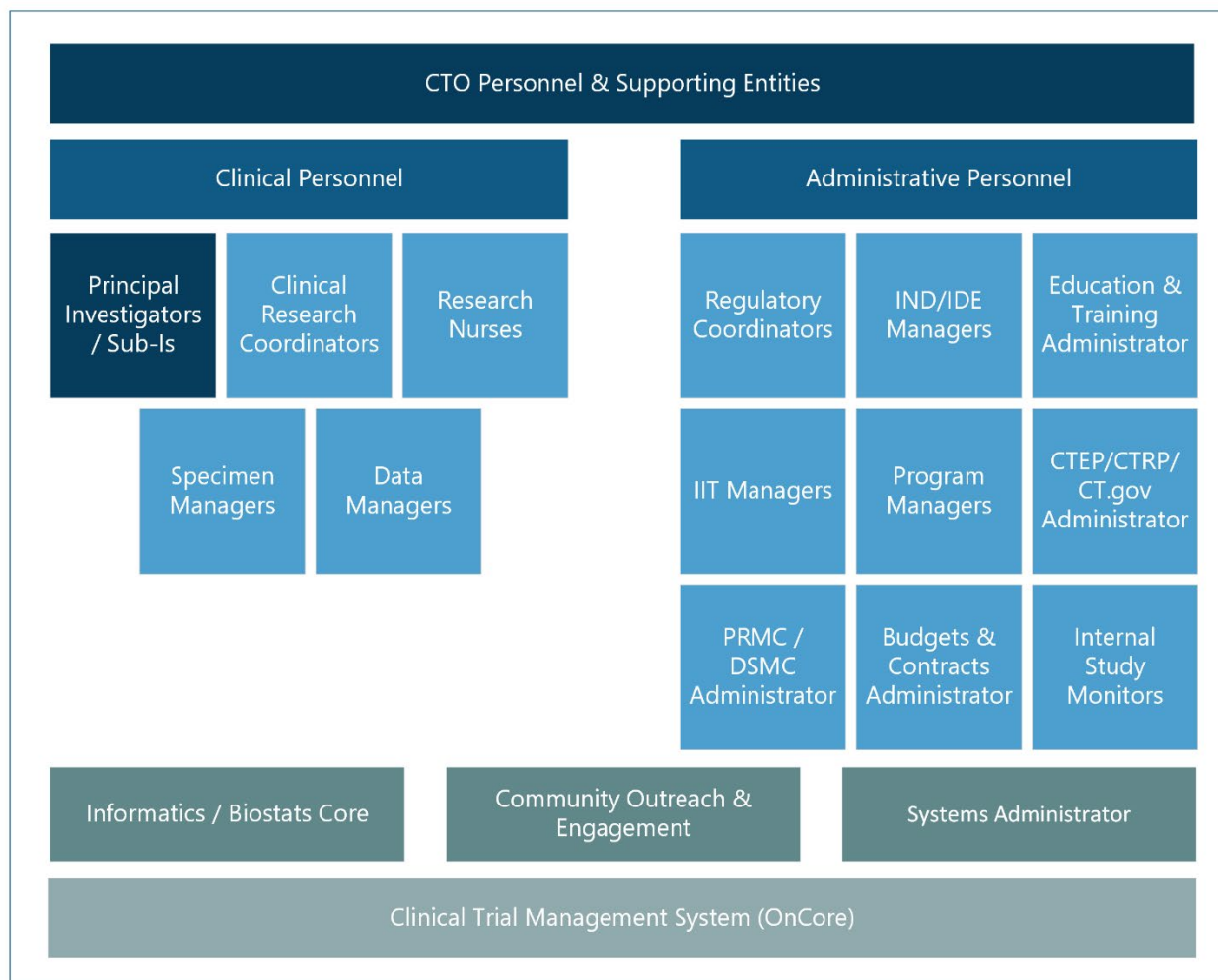
The CTO Administrative Director (CTO AD) reports, directly or indirectly through a senior leader, to the GWCC Director. The CTO AD is responsible for oversight of CTO personnel to ensure proper conduct in coordinating, facilitating, and reporting. This includes ensuring compliance with GWCC Standard Operating Procedures (SOPs) and overseeing the day-to-day operations of the CTO.

The CTO AD should not be a voting member of the PRMC nor the DSMC but can facilitate the operations of these committees.

2.4. CTO Personnel

GWCC investigators and CTO personnel perform the duties required for proper Clinical Protocol and Data Management (CPDM) functions. This includes trial management services such as clinical coordination, regulatory management, data entry, protocol development, IND/IDE support, budget and contract development, financial management, quality control/quality assurance, CTMS maintenance, etc. Services provided by CTO personnel generate the information necessary for the PRMC and DSMC to perform oversight responsibilities. CTO personnel also provide administrative support to the PRMC and the DSMC.

The CTO personnel are vital to the day-to-day facilitation and tracking of research, including the routing of proposed trials to ensure timely activation. CTO personnel have responsibilities with respect to the [Protocol Review and Monitoring System \(PRMS\)](#) and [Data and Safety Monitoring](#). CTO personnel includes, but is not limited to, the Research Nurses, Clinical Research Coordinators, Regulatory Coordinators, Research Data Managers, IIT Managers, and Program Managers. PIs may delegate responsibilities to CTO personnel for facilitating the research. CTO personnel with delegated responsibilities for a trial are considered "study personnel."



Responsibilities of CTO personnel and support staff include assisting the PI and CTO with:

- Implementing protocols and ensuring protocol compliance
- Consenting and screening subjects
- Documentation of adverse events, serious adverse events, and unanticipated adverse device effects
- Documentation of protocol deviations and unanticipated problems
- Data entry into case report forms (CRFs)
- Preparing regulatory submissions to GWCC oversight committees and the IRB
- Maintaining regulatory documentation
- Preparing subject and regulatory documentation for monitoring visits and audits
- Preparing and submitting DSMC Interim Study Reports
- Providing education to CTO personnel
- OnCore data entry for accrual and regulatory tracking
- Cancer Therapy Evaluation Program (CTEP) registrations
- Tracking institutional training requirements
- ClinicalTrials.gov reporting
- IIT protocol and consent development

- Participating in or conducting Site Initiation Visits (SIVs)
- Developing study manuals
- Designing IIT case report forms
- Coordinating day-to-day operations of IITs
- Managing INDs and IDEs
- Reviewing monitor visit reports from all types of trials

2.5. GWCC Internal Study Monitors (ISMs)

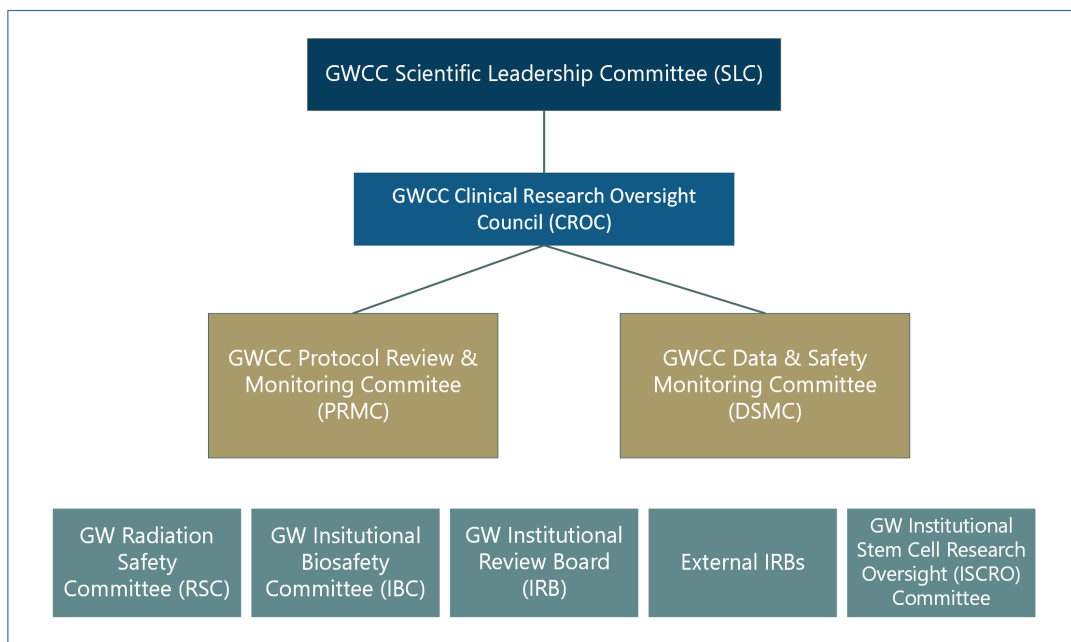
The GWCC Internal Study Monitors (ISMs) play a significant role in quality assurance. ISMs are not considered CTO personnel; ISMs are part of the GWCC Quality and Education Group. Monitoring procedures assure the accuracy of study data, protocol compliance, investigational product accountability, and proper essential document maintenance. ISMs are trained in federal regulations, local SOPs, IRB policy, and Good Clinical Practice to perform their duties.

2.6. Clinical Trial Management System (CTMS) – OnCore

OnCore is the central database of protocol-specific data and is used for the tracking and reporting. Personnel responsible for CPDM functions are required to update OnCore contemporaneously. Use of OnCore is vital for proper oversight of trials, as well as assessing CTO operations.

3. GWCC Research Oversight System

The GWCC has a comprehensive infrastructure to ensure robust oversight and support of clinical research performed by GWCC investigators. The oversight system includes GWCC committees as well as external committees and review boards. This organizational chart includes the committees which are described in detail in the following sections.



This section provides information on the purview, roles, and responsibilities of the individuals, committees, and components of GWCC's research oversight system. The system includes overseeing, facilitating, managing, tracking, reviewing, reporting, and data and safety monitoring of research. Oversight and monitoring of clinical trials exist on a continuum, ranging from monitoring by the PI individually to monitoring by a committee. Monitoring activities will be conducted by individuals and groups with proper expertise to review the research and make the required assessments and determinations.

Data resulting from CPDM functions allows leadership to monitor the timely activation, progress, and completion of trials. Activation timelines will be assessed regularly by CTO leadership; process improvement suggestions will be made to the SLC as needed.

Committee charters, SOPs, and rosters include finer details on membership, roles, responsibilities, review criteria, procedures, and determinations to be made.

All official determinations and recommendations made by Chairs and committees will be documented in writing. If necessary due to urgency, determinations and recommendations may be relayed orally or via email in lieu of a formal letter or memo, but formal written documentation must follow.

Confidentiality

As a condition of their appointment, members of all committees are expected to maintain confidentiality, inclusive of committee deliberations, recommendations, findings, study results, and investigator correspondence. Other individuals involved in the administration of the PRMC and DSMC (e.g., committee administrators) are also required to maintain confidentiality. Interim and outcome results are to be kept particularly confidential. To maintain confidentiality, attendance is limited to committee members and administrative personnel responsible for the functions of the committee, unless an individual is invited for a specific purpose. Internal and external individuals, including Clinical Research Team leaders, PIs, study personnel and/or other CTO personnel, may be invited to attend meetings on an as needed basis to present studies or provide input and/or insight to the committee. The invitees must not remain present for the committee deliberations or votes.

Institutional training

As required by GWU, all investigators and personnel involved in the oversight and/or conduct of clinical trials at GWCC are required to complete training prior to working on any trials. This includes training on Good Clinical Practice (GCP), human subjects protection, and the Health Insurance Portability and Accountability Act (HIPAA). Refresher training may be required at regular intervals. All personnel must remain current on required training. The GW Office of the Vice President for Research (OVPR) is responsible for ensuring investigators complete OVPR-required training. The OVPR holds the PI responsible for ensuring all study personnel working under the PI complete the required research training. Training and credentials of investigators and personnel will be tracked by CTO personnel.

Training on internal CTO policies is provided internally on an ongoing basis.

COI training: GWU personnel must complete training and ensure compliance with the GWU policies on Conflict of Interest (COI) and Conflict of Commitments (COC). The GWU policy requires financial Conflict of Interest (FCOI) training for investigators engaged in PHS-funded research. All applicable individuals must complete the training. GWU COI/C policies can be found on the GWU Office of Ethics, Compliance, and Risk website.

Delegation of Monitoring Activities to External Organizations

The GWCC may transfer monitoring activities to external organizations, e.g., a Contract Research Organization (CRO). All monitoring of institutional trials must be consistent with the GWCC Clinical Trials Office SOPs and this GWCC Data and Safety Monitoring Plan, as applicable and regardless of monitoring entity. The transfer of monitoring activities must be documented in writing and include the specific obligations transferred and to whom. Any obligation not covered by the written description shall be deemed not to have been transferred.

Delegation of Sponsor-Investigator Obligations to External Organizations

For trials conducted under an IND, the Sponsor-Investigator may transfer obligations set forth in 21 CFR 312 and 21 CFR 812 to a CRO. The Sponsor-Investigator is responsible to ensure the individuals/entity to which obligations are transferred are properly trained to perform their duties. The transfer documentation must comply with the requirements of 21 CFR 312.23(a)(1)(viii) and 21 CFR 312.52 for drug trials. While 21 CFR 812 does not provide similar details on transfer of obligations, such transfer would require documentation consistent with the requirements in 21 CFR 312. Transfer of the obligations does not exempt the trial from the requirements set forth in this DSMP. Transfer of responsibilities does not exclude the GWCC Internal Study Monitors from performing review of these trials.

3.1. GWCC Scientific Leadership Committee (SLC)

The GWCC is delegated the responsibility of clinical research oversight through the Scientific Leadership Committee (SLC). The SLC oversees the functions of the GWCC’s Protocol Review and Monitoring Committee and the Data and Safety Monitoring Committee. SLC membership includes GWCC leadership such as the Director, ACD of Clinical Investigations, ACD of Administration and Finance, CTO Medical Director, ACD of Population Science and Policy, and representatives from the Medical Faculty Associates (MFA) such as the Chief of the Division of Hematology/Oncology.

The SLC meets at least quarterly and on an ad hoc basis. SLC responsibilities include:

- Approving the George Washington Cancer Center’s Data and Safety Monitoring Plan,
- Constituting the PRMC and DSMC,
- Appointing the committee chairs and members of the PRMC and DSMC, and
- Reviewing both PRMC and DSMC action summaries semi-annually.

The SLC does not have authority over the determinations made by the PRMC and DSMC.

3.2. GWCC Clinical Research Oversight Council (CROC)

The GWCC Clinical Research Oversight Council (CROC) is a governing body for clinical research at GWCC and reports to the Scientific Leadership Committee. The responsibility of the CROC is to ensure compliance and proper conduct of GWCC research by overseeing the policies, processes, and procedures of the PRMC, the DSMC, and CPDM functions.

The committee is chaired by the ACD of Clinical Investigations. Membership reflects the multidisciplinary and inter-departmental involvement of research at GWCC, including senior clinical research leadership, the ACD of Community Outreach and Engagement, the Chairs of the PRMC, DSMC, the CTO Medical Director, and the CTO Administrative Director.

The CROC meets at least quarterly, and on an ad hoc basis. Each meeting must be comprised of individuals with proper expertise and/or authority over the specific topics/issues to be discussed. Internal and external individuals, including Clinical Research Team leaders and individuals who perform PRMS and CPDM functions, may be invited to attend on an as needed basis to provide input and/or insight to the committee.

The CROC has a broad authority to address organizational concerns such as ensuring proper resources and staffing to conduct research at GWCC. The CROC provides guidance for enhancing the policies, processes, and procedures of the GWCC oversight system, as well as identifying and addressing system-wide issues. The committee may identify opportunities for process improvement and propose solutions. The committee may develop and/or revise policies, and create Working Groups as needed. Policies approved by CROC must receive final approval by the GWCC Director prior to implementation.

Working Groups do not have set requirements nor set membership. As needed, the CROC will determine the need for a Working Group and determine tasks. Working Groups will include individuals with expertise relevant to the topic to be addressed.

The CROC may meet with Clinical Research Team leaders to review the team's research portfolio, research activity, enrollment data (including race, ethnicity, and gender), and provide recommendations for improvement. The CROC may make recommendations to the PRMC regarding underperforming trials.

The CROC does not have authority over the determinations made by the PRMC and DSMC.

3.3. Investigators, Clinical Research Teams, & CTO/Study Personnel

Principal Investigators, Sub-Investigators, Clinical Research Teams, and CTO/study personnel have responsibilities that apply to both PRMS and CPDM functions.

Principal Investigators and Sub-Investigators

The PI of a clinical trial has the ultimate responsibility for oversight and compliance in all aspects of the trial. The PI may delegate tasks, but not responsibilities, to CTO/study personnel, including to Sub-Investigators. The PI is responsible to ensure study personnel to which tasks are delegated have the proper knowledge and scope to perform the delegated tasks. Delegation of tasks must be documented in writing. Regardless of who carries out a study-related activity, the PI is accountable for ensuring the task is conducted in compliance with all applicable regulations and policies.

Clinical Research Teams

Clinical Research Teams should meet at least monthly. CRTs typically identify potential trials for activation at GWCC. There is no set quorum for CRT meetings. CRT meetings will have a formal agenda and minutes will be taken. Should a scheduled meeting not occur, the reason must be documented and maintained in the CRT files.

CTO & Study Personnel

CTO personnel assist Clinical Research Teams and Investigators by performing CPDM functions. To best serve investigators and the CTO, timely and accurate data entry into the OnCore CTMS is required. Individuals with delegated responsibilities for a trial must comply with applicable regulations and policies. Study personnel perform the tasks which are delegated to them by the PI.

The CTO Administrative Director, or other individual as assigned by the CTO Administrative Director, will routinely review monitoring visit reports from all types of trials, including industry-sponsored, federally funded, and GWCC IITs. Review of monitoring reports may identify any patterns that may lead to safety issues and/or noncompliance. To ensure proper follow up, applicable individuals and/or entities will be notified of any issues identified.

3.4. Protocol Review & Monitoring System (PRMS)

The goal of the GWCC Protocol Review and Monitoring System is to ensure that trials activated at the GWCC meet the center's priorities, fulfill the standards for scientific merit, are feasible to be conducted at the GWCC, are appropriately designed, and include a proper data and safety monitoring plan. The PRMS is comprised of two components: The Clinical Research Teams (described [above](#)) and the Protocol Review and Monitoring Committee. The PRMC is the committee charged with accomplishing the goals of the PRMS. Both the CRTs and PRMC perform initial and ongoing review of trials.

3.4.1. Protocol Review & Monitoring Committee (PRMC)

The PRMC serves as an internal peer review. The PRMC's role is to review proposed trials for activation and to monitor the scientific progress of ongoing trials. The initial review for activation assesses scientific merit, feasibility (including staffing and physical resources, as well as availability of the targeted study population), prioritization of the trial in terms of the GWCC goals, expected accrual rates, and study design, including adequacy of both the data and safety monitoring plan and the statistical analysis plan. The PRMC determines the institutional priority and risk level of

trials. The institutional definitions for priority are described in [Table 1](#) and suggested risk levels are provided in [Table 2](#). Prioritization by the PRMC ensures the research portfolio across CRTs is consistent with the goals of the GWCC. The PRMC will ensure research does not exclude individuals of certain ages, races, ethnicities, genders, or other vulnerable or underrepresented populations without proper justification for their exclusion. The PRMC's ongoing review includes monitoring accrual rates, assessing scientific progress, and reviewing amendments that may affect the scientific integrity of a trial.

The PRMC is complementary to IRB review and the PRMC does not duplicate data and safety monitoring functions. Data and safety monitoring functions are separate and distinct. The PRMC uses input from the CRTs to perform their duties, however the PRMC has final authority regarding approval for activation, monitoring, and closing trials that are not progressing appropriately.

To avoid duplication of efforts such as traditional review of trials approved by the NCI's Cancer Therapy Evaluation Program (CTEP) or Cancer Control Protocol Review Committee (CCPRC), such trials may be reviewed by expedited procedures. Per DHHS/NCI, "For multisite institutional trials, the PRMS of the lead site is responsible for the full scientific review of the protocol (if the PRMS has been approved). The other participating sites are responsible only for an expedited review focused on prioritization, competing studies, and feasibility at that site. Should the PRMS at the lead site be conditionally acceptable or unacceptable, participating sites may select a single, acceptable PRMS at a participating NCI-designated Cancer Center to conduct the full scientific review." GWCC may use expedited review consistent with this policy but reserves the right to perform a full committee PRMC review.

The PRMC meets at least quarterly. Full details on the PRMC membership, processes, and procedures for initial and ongoing review are included in the PRMC Charter.

3.5. Data & Safety Monitoring

Data and safety monitoring is a collaborative effort of the PI, study personnel, Internal Study Monitors, and the DSMC. All trials require continuous monitoring by the PI and research team and are subject to periodic and/or unscheduled audits. The DSMC is the committees charged with performing the data and safety monitoring reviews for GWCC IITs.

Details on the DSMC membership, processes, procedures, and determinations to be made are included in the DSMC Charter.

3.5.1. GWCC Data & Safety Monitoring Committee

The GWCC Data and Safety Monitoring Committee is responsible for monitoring all cancer-related interventional GWCC Investigator-Initiated Trials that do not require oversight by a DSMB or are not overseen by another safety monitoring entity. The PRMC determines the level of risk, the data

and safety monitoring (DSM) entity, and the frequency and extent of monitoring (see [Table 2](#) for suggested risk levels, [Table 3](#) for the suggested DSM entity, and [Table 4](#) for the frequency and extent of monitoring).

DSMC membership includes, but is not limited to, physicians, biostatisticians, PhDs, and oncology nurses whose expertise is representative of the research portfolio the committee reviews. Membership may also include pharmacists, administrators, and lay persons, e.g., a patient advocate.

DSMC meetings are set to occur monthly but can be cancelled if there are no studies requiring a scheduled review. Ad hoc meetings may be scheduled when needed.

4. Review and Oversight of Research

4.1. Protocol Review & Monitoring System Reviews

As stated above, the CRT and PRMC perform initial and ongoing reviews. This section describes the CRT and PRMC reviews.

The initial review of research proposed for activation involves two stages: The first stage is performed by the CRT and the second stage by the PRMC.

Note: Single-Patient IND (SPIND) are exempt from CRT and PRMC review since they are considered treatment (i.e., they are not research) and not designed to answer formal scientific questions. If multiple patients will be enrolled to an Expanded Access Protocols, CRT and PMRC review are required.

4.1.1. Clinical Research Team Initial Review

The CRT reviews proposed trials for feasibility, prioritization, scientific quality, and appropriateness for the CRT portfolio. The CRT will either endorse the trial for activation or reject the trial. For each study that is reviewed by the CRT, the Clinical Research Team Trial Review Form (CRTTR) is completed. The CRTTR collects the information necessary for the PRMC to conduct the second stage of initial review. The initial CRT review and CRTTR form can be completed during the in-person CRT meetings (including remote attendance), or input provided by CRT members outside of the CRT meetings.

The CRT and PI must ensure that the study design is adequately described within the protocol. The protocol must include a description of the research question, disease and intervention background, the rationale for the research study, clear eligibility criteria, a valid statistical analysis plan (including a sample size justification and power calculation), description of the agents/device or intervention involved, a description of the planned correlative studies (if applicable), and a comprehensive data and safety monitoring plan.

At a minimum, the CRT makes determinations on the following:

- Is the trial feasible to be conducted at GWCC?
- Is the subject population available in order to accrue a sufficient number of participants?
- Does GWCC have the appropriate resources to conduct the trial?
- Is the trial appropriate for the CRT portfolio?

If endorsed, the CRT will determine:

- The priority level,
- Which Investigator will serve as PI, and
- The accrual goal.

For trials that are endorsed for activation, the CRTTR is provided to the PRMC. For rejected trials, the reason for rejection is documented on the CRTTR, and the form is maintained in the CRT files.

4.1.2. PRMC Initial Review

For the second stage of the initial review, the PRMC uses the CRTTR provided by the CRT and the study documents (protocol, etc.) to assess feasibility, scientific integrity, study rationale, and study design. Additionally, the PRMC confirms the institutional prioritization and the inclusion of an appropriate DSMP and determines the risk level. The risk level is commensurate with the size and complexity of the trial based upon the nature of the intervention, the phase of the protocol, and the potential risks to subjects. The risk level is determined by multiple factors including, but not limited to: Trial phase, expected accrual, trial complexity, whether the trial is conducted under an IND/IDE, and PI experience leading clinical trials. For IITs, the risk level determines the data and safety monitoring requirements, including the frequency and extent of monitoring.

At a minimum, the PRMC initial review includes the following:

- Confirmation of Institutional Priority (per [Table 1](#))
- Confirmation of appropriate fit into GWCC research portfolio
- Confirmation of Feasibility
- Availability of the subject population
- Availability of other resources necessary to facilitate the trial
- Confirmation of the [Protocol Requirements for Certain Types of Trials](#)
- Confirmation of an appropriate biostatistical plan
- Approval of the study's data and safety monitoring plan
- Determination of risk level (see [Table 2](#))
- Determination of data and safety monitoring entity (see [Table 3](#))
- Determination of the frequency and extent of study monitoring (see [Table 4](#))

- Assessment of inclusion of individuals across the lifespan, women, minorities, special/vulnerable, and underrepresented populations, including whether an appropriate plan is included in the protocol, when warranted

The PRMC approves or rejects the trial. The PRMC approval confirms that the trial can be activated at GWCC. The PRMC determination is provided to the PI and relevant CTO personnel.

4.1.2.1. Institutional Priority Definitions

[Table 1](#) provides an overview of the institutional priority level of trials by type/source. During initial review, the CRT documents the priority level on the CRTTR and the PRMC makes the final determination of priority level.

Table 1: Institutional Priority	
Protocol Type/Source	Priority Level
Externally peer-reviewed IITs (e.g., federally funded grants, including P01, R01, U01, SPOREs, or funded by other peer-reviewed entities)	High
IITs that are unfunded or are supported by non-federal entities	Medium High
National group trials (i.e., NCTN, including ECOG, SWOG, NRG, etc.)	Medium
Industry-sponsored trials	Low

4.1.2.2. Risk Level Definitions

The PRMC is charged with determining the risk level. [Table 2](#) provides the suggested risk level for the study types/examples listed. The PRMC ultimately determines the risk level based on the nature of the research and therefore, may not be consistent with the information in [Table 2](#). For any type of protocol that is not defined in the table, the PRMC will use [Table 2](#) as guidance to determine the risk level. The risk level determines the level of oversight requirements. Based on the PRMC’s risk level determination, the frequency and extent of monitoring will be consistent with the information in [Table 4](#), unless specified otherwise by the PRMC. The determined risk level does not preclude the PRMC from requiring increased or decreased frequency or level of review regardless of the study types/examples provided in the table below.

Table 2: Suggested Risk Level Definitions & Examples	
Risk Level	Risk Level Definitions/Examples
High risk (greater than minimal risk)	<ul style="list-style-type: none"> • Clinical trials of high complexity, high potential for toxicity, or those that require a high level of administrative oversight. • Phase I studies conducted under an IND or IDE • All therapeutic interventional investigator-initiated trials*

Table 2: Suggested Risk Level Definitions & Examples

Risk Level	Risk Level Definitions/Examples	
	<ul style="list-style-type: none"> • Trials involving high-risk clinical procedures performed solely for research purposes • Trials involving gene therapy, cellular immunotherapy, or other areas designated by NIH as high-risk • Therapeutic trials targeting special or vulnerable populations 	<ul style="list-style-type: none"> • All IND/IDE trials where GWCC holds IND/IDE • All Significant Risk (SR) device studies
<p>Moderate risk (greater than minimal risk but not considered high risk)</p>	<ul style="list-style-type: none"> • Clinical trials with potential of greater than minimal risk to participants, which do not meet the definition of high-risk trials. • Trials that involve a procedure (e.g., research biopsies, imaging with exposure greater than routine care, etc.) that may involve greater than minimal risk as compared to that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations. 	<ul style="list-style-type: none"> • Trials that are not in the high-risk category that involve therapeutic interventions* • Phase II trials • Phase III trials • IND exempt trials • Nutritional studies that involve interventions • Behavioral studies that involve interventions • Non-Significant Risk (NSR) and 510(k) device studies
<p>Low risk</p>	<ul style="list-style-type: none"> • Studies that represent a minor increase over minimal risk • Studies involving certain invasive procedures • Certain minimal risk studies involving special or vulnerable populations • Minimal risk studies (minimal risks, per 45 CFR 46.102(j), means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. • Studies that fall in the categories for expedite review by an IRB, per the 1998 OHRP Expedited Review Categories. 	<ul style="list-style-type: none"> • Studies involving non-therapeutic interventions • Observational, behavioral, and epidemiological studies • Diagnostic or screening trials involving minimal risk procedures • Biorepositories • Studies using non-invasive procedures • Studies using venipuncture within the limits of 1998 OHRP Expedited Review Categories • Survey research
<p>Exempt from DSMC oversight</p>	<ul style="list-style-type: none"> • Ancillary studies • Correlative studies • Expanded Access Protocols (EAPs) • Basic science protocols which utilize externally purchased publicly available established cell lines or include the independent collection and/or use of orphan tissues. 	<ul style="list-style-type: none"> • Lab-based trials using data linked to a patient to assess clinical outcomes and response to therapies • Treatment of a patient via a single-patient IND (SPIND – compassionate use)

*This includes treatment, supportive care, and prevention trials

4.1.2.3. Protocol Requirements for Certain Types of Trials

Phase I Dose-Escalation Trials

For studies intending to define the dose-limiting toxicity (DLT) of novel agents or combinations of drugs, the data and safety monitoring plan in the protocol must clearly define the dose-limiting toxicities, the rules for dose escalation, stopping rules, and definition of maximum tolerated dose (MTD).

Phase II Trials

Phase II trials, where appropriate, should include early stopping rules for prospectively defined undesirable events. The stopping rules must clearly define the events in question, the frequency with which the stopping rule will be monitored, and the threshold for stopping or modifying the trial. The trial should also contain stopping rules for lack of efficacy where appropriate.

Blinded Trials

All masked studies should describe the randomization schema/procedures as well as the specific criteria and procedures for unmasking. If a DSMB is not proposed, the protocol should designate individuals with access to unmasked data.

4.1.2.4. Inclusion of Minority, Underrepresented, & Special Populations

The GWCC is dedicated to diversity of participants in GWCC research. Per NIH guidelines, women and members of minority groups and their sub-populations, and individuals across the lifespan must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided describing why inclusion is inappropriate. Diversity in clinical trials goes beyond race and ethnicity to include other underrepresented and/or underserved populations defined by demographics such as sex, gender identity, age, socioeconomic status, disability, pregnancy status, lactation status, and co-morbidity. Eligibility criteria and trial design should not be so restrictive as to exclude these populations unless scientifically or clinically necessary to do so.

Initial PRMC review assesses the inclusion of these populations and/or any justification for excluding such. Diversity plans may be requested for individual trials.

Age, gender, ethnicity, and race will be tracked in OnCore. Oversight committees may review this information to identify lack of enrollment of these populations and help identify how to reach these populations within the catchment area.

Additional safeguards may be necessary if a study targets subjects likely to be vulnerable to coercion or undue influence. Compliance with the Office for Human Research Protections

(OHRP) 45 CFR 46 Subparts is required when children (individuals under the age of 18), pregnant women, human fetuses, neonates, and/or prisoners are included in the research.

4.1.3. PI & Study Personnel – Study Activation & Ongoing Review

Principal Investigators, Sub-Investigators, and study personnel are responsible for conducting and facilitating the trial while also maintaining safety and compliance throughout the life of the trial. The requirements outlined in this section apply to all types of trials (i.e., IITs, industry trials, and nationally funded trials).

4.1.3.1. PI & Study Personnel Requirements Prior to Activation

The PI must ensure all required approvals are gained prior to activating the research. The PI must also ensure protocol-specific training has been provided to all study personnel. Training prior to activation is typically provided at a Site Initiation Visit (SIV). Repeat SIVs or training sessions can occur at any time.

For IITs, if required, the PI is responsible for establishing an independent Data and Safety Monitoring Board (DSMB) prior to activation.

4.1.3.2. PI & Study Personnel Ongoing Review

The PI has the responsibility for continuous monitoring of the conduct and safety of the trial. This includes continuous, real-time monitoring to ensure timely and accurate data entry, prompt event reporting, identification and review of protocol deviations, timely submissions to oversight entities (internal and external), and assessing progress of the trial, including accrual. The PI must report all adverse events (AEs), serious adverse events (SAEs), unanticipated adverse device effects (UADEs), noncompliance (including deviations), and unanticipated problems (UPs) per protocol/sponsor requirements, per applicable local and federal policy/regulation, and per this DSMP. If an FDA Risk Evaluation and Mitigation Strategy (REMS) exists for a drug, the PI must ensure the REMS is followed. The PI must ensure proper follow up on queries, findings, and action items identified by oversight entities and study monitors.

For the PI to fulfill their responsibilities, the study personnel and other CTO personnel must perform their duties in a timely and compliant manner. As part of continuous monitoring, PIs/Sub-Is regularly meet with the study personnel including Research Nurses, CRCs, Regulatory Coordinators, and other CTO personnel. These meetings are used to discuss study progress, active subjects, deviations, compliance, corrective and preventative action plans (CAPAs), protocol amendments, status of regulatory submissions, and other topics as applicable. These meetings do not have formal agendas or quorum requirements.

Ongoing trials may be discussed at CRT meetings as needed. Low accrual notices may prompt discussion to determine if the accrual goal remains feasible, if changes to accrual goals are

needed, or determine if the trial should not continue. Other milestones or issues may be addressed with the CRT, when appropriate.

4.1.4. PRMC Ongoing Review

The PRMC is responsible for continued oversight of the trial to review the scientific progress, study amendments, continued feasibility, and whether the trial is meeting the accrual goals. The requirements outlined in this section apply to all types of trials (i.e., IITs, industry trials, and nationally funded trials).

Trials are reviewed at least every 6 months. The PRMC has the authority to close a trial that is not meeting the overall goals. For example, the PRMC may close a trial due to low accrual or infeasibility to complete the trial.

If the PRMC identifies issues related to scientific progress, feasibility, or that the trial is not meeting accrual goals, correspondence is sent to the PI. The PI must provide a response in a timely manner and the PRMC will review the response and make a final determination on whether the trial can continue or not. (Note: Some trials may be exempt from standard accrual expectations, such as trials addressing rare tumors. Accrual for these trials will be assessed on a trial-by-trial basis. Details on accrual monitoring are included in the PRMC Charter.)

Amendments for all types of trials are submitted to the PRMC for assessment of potential alteration to the scientific integrity and/or an alteration deeming a change of the risk level. When appropriate, amendments may be reviewed via the expedite procedures per the PRMC Charter. Should the expedited review determine that there is a potential for alteration of scientific integrity and/or change in the risk level, the amendment will be reviewed by the convened committee. Details on the expedited review process are included in the PRMC Charter.

The PRMC will take appropriate action based on their determinations, which may include suspension or termination of the trial.

4.2. Data & Safety Monitoring

4.2.1. Determination of Data & Safety Monitoring Entity

[Table 3](#) includes recommended data and safety monitoring entity per the sponsor type, the type of trial, and the risk level as determined by the PRMC.

When applicable, the PRMC will require or recommend a trial establish an independent Data and Safety Monitoring Board. The PI, DSMC, sponsor, and/or IRB may also determine an independent DSMB is necessary. Guidelines for establishing and operating a DSMB are found in [Appendix A](#).

[Table 4](#) indicates the minimal recommended frequency and extent of monitoring based on the type of trial and the risk level as determined by the PRMC.

The table below indicates the minimal recommended oversight. The PRMC and/or DSMC may require a higher level of review (entity, frequency, and/or extent) beyond what is minimally recommended. Alternatively, the PRMC and/or DSMC can decrease the requirements, when appropriate.

Table 3: Recommended Monitoring Entity Per Type of Trial and/or Risk Level		
Sponsor	Type of Trial and/or Risk Level Per PRMC	DSM Entity
NCI National Clinical Trials Network	All NCI NCTN trials such as ECOG, NRG, SWOG	Per DSMP approved by NCTN Group
Industry-sponsored trials	All Industry-sponsored trials	DSM entity appointed by the sponsor
GWCC Investigator-Initiated Trials	All randomized Phase III trials supported or performed by NCI	Independent Data and Safety Monitoring Board
	High risk randomized Phase II or III trials	
	Trials with unusually high-risk interventions (such as gene therapy)	
	Therapeutic trials targeting special or vulnerable populations	
	Blinded trials	GWCC Data and Safety Monitoring Committee (unless an independent Data and Safety Monitoring Board is required/recommended)
	High-risk trials not included above	
	Moderate-risk trials	
	Low risk trials	GWCC Data and Safety Monitoring Committee
	Exempt studies	Exempt trials do not require DSMC oversight.

4.2.2. Quality Control Monitoring

As part of the quality assurance system, quality control monitoring of GWCC IITs is performed by the GWCC Internal Study Monitors. The ISMs perform an initial monitoring visit, interim monitoring visits (IMVs) throughout the course of the study, and a close out visit. ISMs are not directly associated with the protocol and do not participate in the conduct of the research. ISMs perform interim monitoring visits at the required intervals (see [Table 4](#)) and provide monitoring visit reports to the PI. ISMs monitor the GWCC site, as well as external sites for multi-site IITs.

The ISMs support the investigator and study team by accessing data accuracy (source document verification), protocol compliance, eligibility verification, AE/SAE reporting, general conduct of the

trial, regulatory compliance, test article accountability, and compliance with good clinical practice and with all applicable regulations and local policy. Internal Study Monitors ensure all documentation is Attributable, Legible, Contemporaneous, Original, Accurate, and Complete (ALCOA-C).

Monitoring frequency is determined based on the risk level of the trial as determined by the PRMC. After each monitoring visit, a monitoring visit report is sent to the PI. The monitoring visit report includes information on what was reviewed, a list of any findings, and dates by which the findings must be addressed. ISMs will meet with the PIs when needed, but no less than the intervals per [Table 4](#). PIs are responsible for reviewing the monitoring visit report and providing the report to applicable oversight committees, including the IRB of record if required per policy.

ISMs may also function as auditors. ISMs will not perform auditing on any trial they previously monitored. The PRMC and DSMC can request that ISMs perform an audit of any GWCC trial, including industry-sponsored trials. ISMs may also assist the CTO with inspection readiness.

4.2.2.1. Monitoring Visits

The initial monitoring visit is triggered by the initial subject enrollment and must occur within 2 months (high risk) or 3 months (moderate, low, and minimal risk) after the date the initial subject signed the consent form. The initial visit will include a regulatory review. After the initial monitoring visit, the interim monitoring visits will occur per the schedule in [Table 4](#). All trials require a close-out visit that must occur prior to IRB closure.

If significant inaccuracies and/or compliance issues (including deviations) are noted during the review of the first subjects monitored, 100% of additional subjects are monitored until adequate compliance is observed. After compliance is determined to be adequate, the percentage of subject case reviews will follow the requirements per [Table 4](#). If compliance problems continue, the trial may be suspended or closed permanently by the ACD of Clinical Science or the data and safety monitoring entity.

For each subject case monitored, the monitoring is to include 100% of that subject's case. I.e., all data and activities from the time of signed consent until the subject is off study.

Interim monitoring visits may be skipped if no new subjects have been enrolled since the prior monitoring visit, there are no subjects on the study intervention, and all queries and findings from previous visits have been resolved. Regulatory document review should always be performed on schedule even if the visit does not require subject data review. Test article review can be delayed if there are no subjects on the study intervention or enrolled since the prior review. In that case, test article review would occur on the next regularly scheduled visit where test article accountability is applicable (e.g., new subjects are enrolled).

Monitoring visits should be performed within the window of +/- 15 days. If visits cannot be performed on schedule, the reason must be documented. This can be documented via email to the PI and study personnel, and the email must be saved in the regulatory files.

4.2.2.2. Study Data Cleaning

In addition to continuous monitoring of the timeliness and accuracy of study data, quality control of data entered in Case Report Forms (CRFs) will be performed via data cleaning prior to locking the study database. Data cleaning will involve identification of discrepancies via data validation checks, cross-validation between forms, and detecting missing data. Ideally, constraints will be built into the CRFs to reduce data entry errors. Based on information gained from data cleaning, queries will be issued when needed.

4.2.3. Frequency & Extent of Study Monitoring

[Table 4](#) provides the frequency and extent of study monitoring. These are the minimum requirements (except where noted). More frequent monitoring can occur on an as needed basis. For example, more frequent monitoring of participant data and/or the test article inventory may be warranted for high enrolling trials. Additional or more frequent monitoring can be requested by the PI, ISM, PRMC, or DSMC. Alternatively, the DSMC may decrease the frequency or extent of monitoring with proper justification.

Any trial of any risk level can be monitored or audited on a for-cause basis at the request of the PI, ISM, PRMC, or DSMC. The extent of for-cause monitoring or auditing will be decided by an appropriate individual or committee with oversight responsibilities.

Table 4: Frequency and Extent of Study Monitoring											
Monitoring Activity Risk Level	DSMC Review Frequency	Monitoring Visit Frequency ¹	ICF & PHI Auth Review	Eligibility Review	Subject Case Review ²	SAEs/ UADEs/ deviations/ UPs	Endpoint -Related Data	Regulatory Document Review	Test Article Accountability	Specimen Disposition	Meet with PI
High risk	Monthly	Every 2 months	100%	100% (1 st 3 subjects)	100% (1 st 3 subjects)	100%	100%	Every 4 months	Every 4 months	100%	Every 6 months & as needed
				50% (4 th subject+) ³	50% (4 th subject+) ³						
				50% (4 th subject+) ³	Gene therapy trials: 100% of ALL subjects for at least the 1 st cycle						
Moderate risk	Every 3 months	Every 3 months	100%	50% (1 st 3 subjects)	50% (1 st 3 subjects)	100%	100%	Every 6 months	Every 6 months	100%	Every 6 months & as needed
				20% (4 th subject+) ³	20% (4 th subject+) ³						
Low risk	Annually ⁴	Every 6 months	100%	20%	20%	N/A	100%	Annually	Every 6 months	100%	Annually & as needed
Exempt	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

¹ The initial monitoring visit is triggered by the first subject enrollment and will include a regulatory review. The initial visit occurs within 2 months of the consent date for high-risk trials and 3 months for moderate, low, and minimal risk trials.

² If significant inaccuracies and/or compliance issues (including deviations) are noted during the review of the first subjects monitored, 100% of additional subjects are monitored until adequate compliance is observed.

³ For the 4th subject+, the percentage is based on the enrollment at the time of the monitoring visit. If 2 or fewer subjects have been enrolled since prior review, both subjects will be reviewed.

⁴ After initial DSMC review, low risk trials of other protocol types, e.g., ancillary, supportive care, etc., may have the annual review requirement waived by the DSMC.

4.2.4. DSMC Reviews & Determinations

The DSMC Interim Study Report is submitted by the PI to the DSMC. The report provides sufficient information for the DSMC to assess safety, conduct, and progress. DSMC review may involve raw data, when appropriate. Each DSMC review may include a review of:

- Cumulative safety data
 - Depending on the size and complexity of the trial, AE data may be reviewed by statistical comparison of treatment groups.
- New safety information since prior review, including SUSARs
- Enrollment progress
 - This includes enrollment rate and subject demographics
- Overall study progress
- Protocol deviations
- Unanticipated problems
- Summary of SAE reports
- ISM visit reports
- Data compliance (completeness, timeliness, accuracy)
- Study endpoint/outcome data
- Any interim analysis
- Revisions to the study protocol
- Internal or external auditing reports (including audits of external sites involved in a GWCC investigator-initiated multi-site trial)

Other study progress markers will be reviewed as applicable to the specific protocol. For multi-site trials, aggregate data across all sites will be reviewed.

If the DSMC determines more frequent Internal Study Monitor visits and/or DSMC reviews are necessary (e.g., for reasons such as high accrual rate or issues identified that may affect subject safety) the reason(s) for increased review will be provided in writing to the PI. Alternatively, if the DSMC determines a decrease in frequency or extent is acceptable, the reason(s) for decreased review will be provided to the PI in writing.

DSMC review continues until enrollment has closed and all subjects have stopped the study intervention, unless the DSMC requires continued review for issues related to data and/or safety, e.g., data quality issues, lack of response to data queries, etc.

DSMC determinations are provided to the PI in writing and the PI is required to provide the determination to applicable oversight entities, if necessary. The PI must provide a response to DSMC requests for additional information in a timely manner.

DSMC determinations include:

- Approved to continue without modification
- Approved to continue with the modification(s)
 - The study may continue only if the PI amends the trial per DSMC requirements. (Typically, the PI needs to initiate the changes and report such to the DSMC at the next regularly scheduled review. The DSMC may set a sooner response deadline.)
- Approved to continue with stipulations/more information requested
 - The study may continue pending PI response to DSMC questions, concerns, and/or recommendations. (Typically, the PI needs to provide a response by the next regularly scheduled review. The DSMC may set a sooner response deadline.)
- Suspend the study or suspend specific study activities
 - The reason(s) for suspension and the activities to be suspended will be provided to the PI.
- Terminate the study
 - The reason(s) for termination will be provided to the PI.
- More information required
 - A determination to continue or stop the study cannot be made without additional information. (This determination may require immediate response from the PI and the trial return to the committee at the next regular meeting, an ad hoc meeting, or administrative review by the Chair to make a final determination.)

DSMC determinations may include requests and recommendations for updates to the study documents.

4.2.4.1. DSMC Study Suspension or Termination

The DSMC has the authority to suspend some or all activities (including suspension of enrollment), or terminate a trial based on futility, unacceptable risks, or other reasons within its purview. A DSMC determination of suspension (overall or partial) or termination will be provided to the PRMC, IRB, and the GWCC Director. When applicable, the determinations must be provided to other local and federal oversight entities and/or the sponsor or supporting entity. Suspension or termination of an NCI funded study requires notification to the NCI grant Program Director.

4.2.5. DSMC Review of SAEs and UADEs

The DSMC will review SAEs and UADEs at each planned review. The DSMC will determine if there is an overarching concern (i.e., the reports indicate an unexpected risk or an increase in frequency or magnitude of an already known risk) and may request revision to the study documents. If PIs fail to meet the SAE reporting requirements, the DSMC may require a CAPA be submitted for review and approval.

4.2.6. DSMC Review of Noncompliance, Protocol Deviations, & Unanticipated Problems

The DSMC will review noncompliance, protocol deviations, and unanticipated problems at each planned review. DSMC will determine if there is an overarching concern affecting the rights and welfare of subjects or whether the noncompliance, protocol deviations, or unanticipated problems affect the integrity of the study data, individually or as a whole. The DSMC will determine whether a CAPA is needed. The DSMC may request revisions to the study or study documents.

4.2.7. DSMC Review of Monitoring Visit Reports

GWCC IITs

Monitoring visit reports for GWCC IITs must be provided to the DSMC with the DSMC Interim Study Report for each regularly scheduled review as noted above.

Independently monitored trials

For trials that are independently monitored by an external sponsor or sponsor-designated contractor (e.g., a CRO), monitoring visit reports must be provided to the DSMC contemporaneously. The reports will be reviewed at the next regularly scheduled meeting.

4.2.8. DSMC Oversight of Industry Sponsored Trials

Data and safety monitoring of industry-sponsored trials is performed by the sponsor, but the DSMC may monitor and/or audit these trials and monitoring visit reports are provided to the DSMC.

A plan for the GWCC DSMC to monitor an industry-sponsored trials is based on the level of risk and complexity of the trial and is determined by the PI and PRMC. A copy of any audit reports, internal or external, are provided to the DSMC.

4.2.9. DSMC Oversight of Trials Overseen by an Independent DSMB

For trials that are overseen by a DSMB, the study reports and DSMB determinations are submitted to the DSMC contemporaneously. The reports and determinations will be reviewed at the next regularly scheduled meeting.

4.2.10. DSMC Oversight of Corrective and Preventative Action Plans

The DSMC will review and monitor the implementation of Corrective and Preventative Action (CAPA) Plans. When a CAPA is required, the PI and study team are responsible to develop the CAPA and, when necessary, in consultation with the DSMC. The DSMC must review and approve the CAPA. The PI and study team must ensure the CAPA is implemented as soon as possible. In addition to the DSMC, GWCC ISMs, relevant CTO personnel, and/or other applicable oversight committees may be responsible for monitoring CAPA implementation and compliance.

4.3. Institutional Review Boards

The GW IRB, NCI CIRB, or commercial IRB may serve as the IRB of record for GWCC trials. The responsibility of the IRB is to protect the rights and welfare of subjects. All human subjects research that does not qualify for exemption per 45 CFR 46 must be IRB approved prior to activation. IRB review includes, but is not limited to, an assessment of the risk/benefit ratio (that risks are minimized and risks are reasonable in relation to anticipated benefits), whether study procedures are consistent with sound research design, and if there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

It is recommended that the Principal Investigator of a cancer-related investigator-initiated trial gain approval from the PRMC prior to submission to the IRB of record. This will prevent the PI from having to resubmit revised protocols to both review committees.

An IRB has the authority to approve, require modifications to secure approval, or disapprove human subjects research, including when reviewing proposed changes to previously approved research. IRB continuing review intervals are set by the IRB per the OHRP regulations, 45 CFR 46. IRBs also have the authority to suspend or terminate previously approved research that is not being conducted in accordance with the IRB's requirements or unexpected serious harm to subjects is identified. The IRB of record will follow its policy for prompt notification of suspension or termination to appropriate institutional officials, OHRP, FDA, or other entities, as applicable. If the IRB suspends or terminates a study, the PI must notify the PRMC, DSMC, or applicable local and federal oversight entities, and the study sponsor, as applicable.

PIs are responsible for notifying the IRB of PRMC and/or DSMC determinations that affect the status of the research.

4.4. Other GW Research Oversight Committees

Trials requiring review and/or approval by other GW oversight entities will be routed per the requirements of such entities. This includes entities such as the GW Institutional Biosafety Committee and GW Radiation Safety Committee. Trials cannot be activated at GWCC without the required reviews and/or approvals.

5. Management & Oversight for Special Circumstances

5.1. IIT Multi-site Trial Management

For multi-site IITs, the GWCC Coordinating Center (CC) Principal Investigator is responsible to oversee all participating sites. A plan for compliance and data and safety monitoring across all sites must be included in the study documents. The procedure for central SAE/UADE reporting must be described in the study documents, when applicable. The protocol must name the entity responsible for data and safety monitoring (e.g., the GWCC DSMC, external DSMC, or independent DSMB).

A study manual will be created to document the study processes and procedures to ensure consistency across sites and compliance with the study requirements. A lab manual will be created when applicable.

The CC PI is responsible for awareness of all SAEs/UADEs reported on the trial. The PI and/or other delegated individual, e.g., a Medical Monitor, when applicable, are responsible for contemporaneously reviewing all SAEs/UADEs, including those submitted by internal Investigators (GWCC Sub-Investigators). The CC PI (and other delegated individual, when applicable) will determine if the information deems a revision to any of the study documents (i.e., protocol and/or consent form). (In addition to the CC PI determination, the DSMC may request or require updates to the study documents.)

CTO personnel may serve as the primary liaison between the PI and entities providing support for the trial. For example, a pharmaceutical company providing the study drug and/or financial support for the trial.

Communication between the GWCC CC PI and the sites will involve regularly scheduled teleconferences. The teleconferences will include a discussion of any safety issues that are identified, updates on accrual, and any changes to the study documents.

The IIT Manager will be the main contact for the sites. The IIT Manager will escalate questions and/or issues to the CC PI, or other appropriate individual or entity.

The PI must ensure new information that results in changes to the study documents is distributed to all sites in a timely manner. Safety reports received from the drug/device manufacturers must be distributed to the sites within 15 calendar days of receipt. DSMC/DSMB determinations will be provided to the sites.

At a minimum, subject accrual from all sites must be entered into OnCore for CCSG accrual tracking. Depending on the trial, other information may be required to be entered into the GWCC OnCore for tracking and reporting purposes.

By default, study monitoring will be performed by the GWCC ISMs. Alternatively, an external monitoring entity can be used. When an external entity will be used, the GWCC Data and Safety Monitoring Plan must still be followed unless otherwise specified in the study documents and approved by the PRMC. In cases where GWCC has contracted with a clinical research consortium to perform monitoring of a GWCC multi-site IIT, the extent and frequency of monitoring must occur per this DSMP. As noted elsewhere in this document, any transfer of obligations must be documented in writing.

Participating sites may self-monitor on multi-site Investigator-Initiated Trials for which GWCC is the Coordinating Center. Sites are required to follow the GWCC Data and Safety Monitoring Plan regarding frequency and extent of monitoring unless the site is an NCI Designated Cancer Center with an approved Data and Safety Monitoring Plan. In that case, the site may follow their own NCI-approved DSMP. If a site will self-monitor, this must be specified in the study documents and the external site's DSMP must be submitted to the PRMC for review. This self-monitoring option is only applicable to the monitoring performed by Internal Study Monitors; the GWCC DSMC remains the oversight entity for routine data and safety monitoring.

Monitoring visit reports for the external sites will be sent to the site PI, the GWCC CC PI, and are submitted to the DSMC with the DSMC Interim Study Report.

There are additional requirements for multi-site trials that are conducted under an IND and/or IDE. Refer to the section below titled [IITs Conducted Under an IND and/or IDE](#).

Note: Should a single-site IIT be expanded to a multi-site trial, the trial automatically falls under the multi-site requirements for data and safety monitoring.

5.2. IND Exempt Trials

To be considered IND exempt, the trial must meet **all** the criteria in 21 CFR 312.2(b).

The PI must document that the study meets the criteria for exemption. The IND Exemption Checklist must be completed, signed by the PI, and saved in the study files. The IND Exemption Checklist must be submitted to the PRMC with the study documents for initial review.

Adverse event, serious adverse event, and other reporting requirements in this DSMP still apply to IND exempt studies.

5.3. IITs Conducted Under an IND and/or IDE

When an IIT involves an Investigational New Drug (IND) application and/or Investigational Device Exemption (IDE), the investigator holding the IND or IDE is the "Sponsor-Investigator." Therefore, the GWCC Investigator is also the "Sponsor" and is responsible for compliance with all applicable parts of 21 CFR 312 and/or 21 CFR 812 for both Investigator and Sponsor.

The FDA Form 1572 is required for trials conducted under an IND, and an Investigator Agreement is required for trials conducted under an IDE.

The Sponsor-Investigator must review each SAE (for drug trials) and unanticipated adverse device effect (UADE) that occurs on the trial to determine if it meets the requirements for expedited reporting to the FDA. This includes SAEs and UADEs that are submitted by other local investigators (i.e., Sub-Investigators).

As part of assisting the Sponsor-Investigator with compliance to federal regulations, the GWCC Internal Study Monitors may perform reviews of sponsor documentation and procedures to ensure sponsor responsibilities are being met.

5.3.1. Multi-site trials conducted under an IND and/or IDE

For multi-site trials, an FDA Form 1572 (for INDs) or an Investigator Agreement (for IDEs) must be signed by each external site PI.

In addition to any SAE occurring at GWCC, the Sponsor-Investigator must review each SAE submitted by external sites in a timely manner to determine if the SAE meets the requirements for expedited reporting to the FDA.

The Sponsor-Investigator must ensure information regarding events that occur on the trial that meet the definition of a serious, unanticipated, suspected adverse reaction (SUSAR) for IND studies or unanticipated adverse device effect for IDE studies are distributed to all sites in a timely manner. SUSARs/UADEs received from the drug/device manufacturer (or their delegated CRO) must be distributed to the sites within 15 calendar days of receipt. Information on other relevant events can be provided to the sites at the discretion of the Sponsor-Investigator.

5.3.2. CTO support for IND and IDE Management

CTO personnel will assist with ensuring Sponsor-Investigators comply with their responsibilities per 21 CFR 312 and/or 21 CFR 812. Cancer Center members who file an IND or IDE application must submit a copy of the application and other related documents (communications, safety reports, amendments, annual reports, etc.) to the GWCC Clinical Trials Office. IND/IDE information will be tracked in OnCore and support to the Sponsor-Investigator will be provided as needed, including but not limited to reminders of FDA annual report due dates and reviewing the annual reports prior to submission to the FDA.

5.4. Gene Therapy / Gene Transfer

Trials involving gene therapy or gene transfer must follow the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules. Specifically, Phase I and II gene transfer trials must comply with additional requirements imposed by the NIH Guidelines, e.g., reporting of adverse events to the Office of Biotechnology Activities. The NIH guidelines are found here:

https://osp.od.nih.gov/wp-content/uploads/NIH_Guidelines.pdf

ALL subjects on gene therapy trials are required to be monitored for at least the 1st cycle of treatment. The monitoring plan for gene therapy trials may require increased oversight at the discretion of the PRMC or DSMC.

6. Audits

Independent audits play a critical role in assuring that trials are conducted properly and data are collected, documented, and reported in compliance with the protocol and all local and federal regulations. Audits may include but are not limited to review of subject records, consent process, documentation of informed consent, data quality, regulatory compliance, product accountability, protocol adherence, adequate PI oversight, and compliance with reporting requirements (AEs, SAEs, UADEs, noncompliance, deviations, and unanticipated problems). All trials are subject to the potential for audit, including industry trials. All audit reports, internal or external, are provided to the DSMC.

6.1. Audits Performed by External Entities

Audits may be performed by external entities (i.e., FDA, industry sponsor, NCI). Notification of any external audit must be forwarded to the GWCC Director, ACD of Clinical Investigations, and the CTO Administrative Director immediately. Audit reports must also be provided to the ACD of Clinical Investigations, the GWCC Director, and the DSMC.

6.2. GW Office of Clinical Research Audits & Annual Audit Plan

Audits are conducted by the GW Office of Clinical Research in accordance with applicable regulatory standards. OCR leadership will meet with GWCC leadership and/or CTO personnel to develop an auditing plan for the upcoming year, which can be revised as needed. This will include the list of trials to be audited and will focus on high-risk trials but can include any trial of any risk level. OCR may also perform unplanned audits at any time. The list of protocols to be audited for the coming year is generated based upon a number of factors (e.g., prior audit of the study, risk level of the study, PI experience, etc.). The final prioritization of trials to be audited is reviewed and approved by the ACD of Clinical Investigations.

6.3. GWCC Internal Audits

As noted above, routine or for-cause internal audits may be performed by the GWCC ISMs. Audits may be recommended by a GWCC entity for quality assurance or for-cause.

Audits of cooperative group studies may occur in the interim between the cooperative group audits, i.e., ECOG studies for which audits occur only once every 3 years may be audited by the GWCC ISMs.

For internal audits, the PI will be notified of an upcoming audit which will include the extent of auditing (i.e., regulatory documentation, test article accountability, and which subjects). The auditor will pre-select subjects to be audited. Additional auditing may occur based on findings of the audit; therefore, the extent of the audit is not limited to the initial plan. Exit briefings with the site PI will be conducted at the end of the audit to summarize and discuss findings. This provides an opportunity for the PI and/or study personnel to provide clarification and/or ask questions. A final report will be provided by the auditor to the PI.

For multi-site trials, external sites are also subject to GWCC auditing.

6.4. GWCC Internal Audit Reports

A final, written audit report will be sent to the PI, which will require signature by the PI. The PI is responsible to provide audit reports to the applicable oversight entities. The PI is responsible to ensure follow up on any findings until resolution. The PI may be required to develop and submit CAPAs if necessary.

For multi-site studies, reports resulting from an audit of an external site are sent to the site PI and the CC PI. Audit reports must be provided by the PI to the DSMC. The PRMC and the DSMC have the authority to take appropriate action within their purview based on any significant audit findings.

7. Adverse Events, SAEs, UADEs, Deviations, & Unanticipated Problems

Identifying, documenting, and reporting adverse events (inclusive of SAEs and UADEs), deviations, and unanticipated problems is a component of continuous safety monitoring by the PI. The protocol must document the grading scale to be used for adverse events (e.g., CTCAE version 5.0). Adverse Events should be assessed at every subject visit/contact.

All protocols are required to have a section describing the documentation and reporting requirements for safety data and deviations. The protocol must include specific information on any reporting requirements for subject pregnancy and/or pregnancy of a subject's partner, when applicable.

The following must be documented, and events must be reported if required by institutional, local, and federal policies or regulations, and/or the study protocol:

- Adverse Events
- Serious Adverse Events
- Unanticipated Adverse Device Effects
- Protocol-specific AEs of special interest (AESI)
- Events that are study endpoints
- Protocol deviations/violations
- Exceptions to protocol (planned deviations)
- Changes made to the research without prior IRB approval
- Events or problems that meet the definition of an unanticipated problem
- Other specific events required by the study

Documenting, reporting, and review of AEs, SAEs, UADEs, and deviations will occur in compliance with this DSMP, GWCC CTO SOPs and applicable oversight entities. This includes federal regulations, NIH guidelines, the IRB of record's policies, OHRP, and any other relevant internal or external oversight or supporting entities (e.g., granting agency).

8. Conflicts of Interest

Conflicts of interest and/or conflicts of commitment (COI/C) must be eliminated or mitigated in all steps of the oversight process. The GWCC exists and functions within the structure of the GWU and as such is subject to the University's Conflict of Interest and Conflict of Commitments guidelines and regulatory standards. GWU policies are in line with Public Health Service regulations per 45 CFR 94. GWU has established mechanisms to identify potential conflicts, including annual disclosure requirements, research and sponsored project application questions, and informal communications. See:

<https://compliance.gwu.edu/conflict-interest>

A financial Conflict of Interest arises when a member of the study team is in a position to influence research decisions or trial conduct in ways that could lead directly or indirectly to financial gain or advantage for the study team member or his or her family. Financial interests include payment for services (such as consulting), stock or equity interests, and intellectual property rights.

Conflicts of interest and conflicts of commitment can also include professional interest, proprietary interest, and miscellaneous interest.

All required personnel, including members appointed to committees, must be current on disclosure of financial interests and commitment interests in accordance with GWU policies. Personnel must also disclose any new real or perceived COI/Cs that arise at any time per the requirements of the GWU policies. Upon disclosure of a real or perceived COI/C, GWU policy will be followed for mitigating or eliminating the COI/C. The PRMC and/or DSMC may review the elimination/mitigation strategy and provide input.

Any GWCC-specific COI policies are in addition to GWU COI policies.

8.1. Conflicts of Interest Related to Individual Studies

The primary method for eliminating perceived or real COI/Cs with relation to facilitating a trial is to exclude the individual from being study personnel. Individuals with real or perceived COIs cannot serve as a PI or Sub-I.

Internal Study Monitors must not have a COI/C with the studies they monitor or audit.

8.2. Oversight Committee Conflicts of Interest

The primary method for eliminating perceived or real COI/Cs with relation to the functions of the GWCC oversight committees is for members to recuse themselves during review (discussion and voting) of trials in which they are study personnel or have a significant interest that may influence their decisions regarding a trial. Committee members who are listed as study personnel are, by default, considered to have a COI/C. If the Chair of a committee has a COI/C with a trial under review, the Chair must recuse themselves and another voting member of the committee will serve as Chair during the

review of the trial. Meeting minutes must reflect that the member was recused for the discussion and voting on that trial.

When members are recused, it must be confirmed that quorum is still intact without the recused member(s).

Appendix A: Guidelines for Establishing and Operating a DSMB

1. Membership

- a. Monitoring activities should be conducted by experts in all scientific disciplines needed to interpret the data and ensure participant safety. Clinical trial experts, biostatisticians, bioethicists, and clinicians knowledgeable about the disease and treatment under study should be part of the monitoring group or be available for consultation if warranted.
- b. Voting members may be from within or outside the institution, but the majority should not be affiliated with the institution. Members should view themselves as representing the interest of participants and not that of the institutions. Investigators directly involved with the conceptual design or analysis or treatment/enrollment of the particular trial are not eligible to serve on the DSMB.

2. Meeting Procedures

- a. Frequency: DSMB meetings will be held at least every six months and more often depending on the nature and progress of the trial being monitored.
- b. Elements for Review
 - i. A written summary of status, toxicity and outcome of the clinical trial will be prepared by statistician. The summary will be submitted to DSMB members allowing enough review time prior to meeting.
 - ii. This summary will also address specific toxicity concerns as well as concerns about the conduct of the trial. It may contain recommendations for consideration by the DSMB concerning whether to close the trial, report the results, or continue accrual or follow-up.
- c. Meeting Structure DSMB - Meetings will be divided into three sessions as follows:
 - i. **Open Session** - members of the clinical trial team present review of the trial conduct and answer questions from DSMB members. Focus is on accrual, protocol compliance, and general toxicity.
 - ii. **Closed Session** - Includes DSMB members and the clinical trial statistician(s). The statistician presents and discusses outcome results with DSMB.
 - iii. **Executive Session** - DSMB members only discuss the general conduct of trial, all outcome results including toxicities as described in the protocol, all adverse events and develop recommendations.

3. Recommendations

- a. It is the responsibility of the PI, the clinical trial statistician(s), and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that became available, and any programmatic concerns related to the clinical trial being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to the specific trial.

- b. DSMB recommendations will be given to the PI, the GWCC DSMC, and the sponsor. The DSMB must provide an adequate rationale for any recommendations made to change the trial for other than safety or efficacy reasons or for slow accrual.
- c. The PI is responsible to implement the change recommended by the DSMB as expeditiously as possible.
- d. The sponsor must be informed of the reason for disagreement in the unlikely situation that the PI does not agree with the DSMB recommendation.
- e. The sponsor, DSMB Chair, and PI will be responsible for reaching a mutually acceptable decision about the study.

4. Release of Outcome Data

- a. In general, outcome data should not be available to individuals outside of the DSMB until accrual has been completed and all participants have completed their treatment.
- b. The DSMB may approve the release of outcome data on a confidential basis to the PI for planning the preparation of manuscripts and/or to a small number of others for future trial planning purposes (if applicable).
- c. Any release of outcome data prior to the DSMB recommendation for general dissemination of results must be reviewed and approved by the DSMB.

5. Confidentiality

- a. No communication, either written or verbal, of the deliberations or recommendations of the DSMB will be made outside of the DSMB.
- b. Outcome results are strictly confidential and must not be divulged to any non-member, except as allowed per this document, until the recommendation to release the results are accepted and implemented.
- c. Each member of the DSMB, including non-voting member, must sign a statement of confidentiality.

6. Conflict of Interest

- a. DSMB members are subject to Federal regulations and GWCC's policies regarding standards of conduct.
- b. Individuals invited to serve on the DSMB (voting or non-voting) will disclose any potential conflicts of interest, whether real or perceived, to the PI and the appropriate institutional officials, in accordance with the GWCC COI/C policies. Conflict of interest can include professional interest, proprietary interest, and miscellaneous interest as described in the NIH Grants Policy Statement, Page II-12, and 45 CFR Part 94.
- c. Decision concerning whether individuals with potential conflicts of interest or the appearance of conflicts of interest may participate in the DSMB will be made in accordance with the GWCC COI/C policies.
- d. Potential conflicts, which develop during a member's tenure on a DSMB, must also be disclosed and addressed in accordance with the GWCC COI/C policies.